UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/031,067	07/01/2002	Karim Malik	000487.00011	5996

22907 7590 12/13/2005

BANNER & WITCOFF
1001 G STREET N W
SUITE 1100
WASHINGTON, DC 20001

EXAMINER	
KIM, YOUNG J	

ART UNIT	PAPER NUMBER
1637	

DATE MAILED: 12/13/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/031,067	MALIK ET AL.	
	Examiner	Art Unit	
	Young J. Kim	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 August 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *7,10-12,15-17,19 and 23* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *15-17* is/are allowed.

6)☒ Claim(s) *7,10-12,19 and 23* is/are rejected.

7)☒ Claim(s) *23* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *15 January 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The instant Office Action is responsive to the Amendment received on August 25, 2005.

Preliminary Remark

Cancellation of claims 1-6, 8, 9, 13, 14, 18, 20-22, and 24-38 are acknowledged.

Claims 7, 10-12, 15-17, 19, and 23 are pending and are under prosecution.

Claims recite the term, "tumor" and "tumour" interchangeably. Applicants are advised to use consistent claim language throughout claims for added clarity.

Specification

In the description of the drawing (page 8), the specification refers to Figure 2. Figure 2 discloses nucleotide sequences encompassed by 37 CFR 1.821 through 1.825, but fails to recite its accompanying SEQ ID Identifier. The description of the drawing fails to cure this deficiency.

It appears that SEQ ID NO: 8 should be used to identify Figure 2 in the figure itself or in its description.

Correction is requested.

Claim Objections

The objection of claims 12, 15-17, 19, and 20 for being dependent on canceled claims, made in the Office Action mailed on December 1, 2004, is withdrawn in view of the Amendment received on August 25, 2005, canceling the claim 20, and amending claims 12, 15-17, and 19 to depend from pending claims.

The objection of claims 12, 15-17, 19, and 20 for being in improper multiple dependent format, made in the Office Action mailed on December 1, 2004, is withdrawn in view of the Amendment received on August 25, 2005, canceling claim 20, and amending claims 12, 15-17, and

19 to proper dependencies. Claims 12, 15-17, and 19 are examined on the merits therefore. Any rejections or objection made to these claims would be necessitated by amendment.

Claim Rejections - 35 USC § 112

The rejection of claims 7-11 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter, made in the Office Action mailed on December 1, 2004, is withdrawn in view of the Amendment received on August 25, 2005, canceling claims 8 and 9; and amending claims 7, 10, and 11 to remove the indefinite issues.

The scope of enablement rejection of claims 7 and 11 under 35 U.S.C. 112, first paragraph, for being enabling for a method of disease diagnosis and prognosis in a subject with a Wilms' tumor cancer, wherein said method comprises the determination of the differentially methylated states of a specific nucleotide sequence or sequences in the subject, wherein said specific nucleotide sequence is negative regulatory element or an antisense regulatory region of WT1 gene, does not reasonably provide enablement for the method wherein said method comprises the determination of the differentially methylated states of **any** nucleotide sequence or sequences of **any** gene in a sample, made in the Office Action mailed on December 1, 2004 is withdrawn in view of the Amendment received on August 25, 2005, amending the claims to the suggested-enabling scope.

The rejection of claims 7-11 under 35 U.S.C. as failing to comply with the written description requirement, made in the Office Action mailed on December 1, 2004 is withdrawn in view of the Amendment received on August 25, 2005, amending claims 7, 10, and 11, and canceling the claims 8 and 9.

New Grounds – Necessitated by Amendment

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 7, 12, and 19 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 7 is indefinite for reciting the phrase, "[a] method of Wilm's tumor diagnosis or cancer prognosis in a subject," because it remains indefinite whether the phrase is intending to state that the method is drawn to Wilm's tumor diagnosis or its prognosis; or that the method is drawn to Wilm's tumor diagnosis or prognosis of other form of cancer. For the purpose of prosecution, the former interpretation is assumed. The present rejection is necessitated by amendment adding the phrase, "or cancer."

Claim 12 recites the phrase, "the method comprises determining the methylation state of WT1 NRE comprising SEQ ID NO: 8 or 9..." The instant specification discloses that the nucleotide sequence of a negative regulatory element (NRE) is shown by SEQ ID NO: 9. The specification further discloses that ARR is shown by SEQ ID NO: 8. It is evident that NRE is a portion of the longer ARR. Hence, it becomes indefinite how a shorter region of NRE can comprise SEQ ID NO: 8 (ARR).

Claim 19 is indefinite because it is unclear what the claim is intending to claim – *i.e.,* a product (kit or probe) or a method (assay, monitoring method) (MPEP 2173.05(p)(II), citing *Ex parte Lyell,* 17 USPQ 2d 1548 (B.P.A.I. 1990)).

In addition, claim 19 is rejected under 35 U.S.C. 101 because the claimed is neither drawn to a "process" (method) nor a "machine" (product), but rather embraces or overlaps two different statutory classes of invention set forth in 35 U.S.C. 101 which is drafted so as to set forth the statutory classes of invention in the alternative only.

Claim 19 was previously not further treated on the merits because the claim was improperly multiple dependent. Hence, the instant rejection of claim 19 is necessitated by amendment which placed the claim in proper dependent form.

Rejection – Maintained & Necessitated by Amendment

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Necessitated by Amendment

Claims 7, 11, and 23 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of Wilm's tumor diagnosis/prognosis, wherein the method determines the methylation state of WT1 antisense regulatory region (ARR) and/or WT1 negative regulatory element (NRE), does not reasonably provide enablement for a method of Wilm's tumor diagnosis/prognosis, wherein the method determines the methylation state of a nucleotide sequence(s) **comprising** WT1 ARR and/or WT1 NRE. The specification does not enable any

person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Factors to be considered in determining whether a disclosure would require undue experimentation are summarized in In Re Wands (858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988)). They include (A) the quantity of experimentation necessary, (B) the amount of direction or guidance presented, (C) the presence or absence of working examples, (D) the nature of the invention, (E) the state of the prior art, (F) the relative skill of those in the art, (G) the predictability or unpredictability of the art, and (H) the breadth of the claims.

Breadth of the claims:

The breadth of claims 7, 11, and 23 are drawn to a method of Wilm's tumor diagnosis/prognosis wherein the method determines the methylation state of a nucleotide sequence(s) **comprising** WT1 ARR and/or WT1 NRE.

The instant specification discloses that WT1 gene organized as 10 exons spanning 60,000 bases (page 1, 3rd paragraph). The breadth of the claims, therefore, is drawn to a method of Wilm's tumor diagnosis/prognosis, wherein the method is not limited to the determination of the methylation of WT1 ARR and/or WT1 NRE, but anywhere on WT1 gene which "comprises" ARR and/or NRE. The instant application does not enable a skilled artisan in the discipline to practice the invention commensurate in scope of the claims.

Amount of Guidance:

The instant specification states that the inventors have identified an antisense regulatory region (ARR) of the WT1 antisense promoter and that the ARR is part of a differentially methylated region (page 3, lines 1-2). In addition, the specification discloses that the inventors have found a correlation between the levels of ARR methylation, and the pathological state of human cells (page

3). The specification discloses that in order to determine whether the differential methylation of the WT1 ARR/NRE is accompanied by allele specific expression of the WT1 antisense RNA (WT1-AS), reverse transcription-PCR analysis was conducted (page 13, 5th paragraph). Net increase of WT1-AS expression is disclosed as being observed in Wilm's tumor samples when compared to its expression in a normal sample (page 14, 5th paragraph).

Hence, the specification gives guidance drawn to a method of determining methylation pattern from specific regions of WT1 gene, that is ARR and NRE. The specification, however, is silent on whether methylation patterns in regions other than ARR and NRE found on WT1 gene can be employed in the diangnosis/prognosis of Wilm's tumor.

Working Example:

The instant specification discloses working examples drawn isolation of a partial WT1 cDNA was used as a probe to screen a cDNA library to sequence a full-length cDNA. The specification discloses that the 700 base pair fragment from the 5' terminus of the full-length cDNA was used to probe a genomic library, followed by the subcloning of the genomic clones corresponding to 5' end of the WT1 gene (page 9, 1st and 2nd paragraph). Digestion of the corresponding DNA with methylation-specific enzymes results in differential banding pattern when separated on electrophoresis (Figure 1(D) and page 10, 1st and 2nd paragraphs). The region of digestion is disclosed as being in the intronic region of Figure 2 (page 9, bottom paragraph), wherein the region is disclosed as WT1 ARR (page 8, description of Figure 2) consisting of 1850 base pairs (also SEQ ID NO: 8).

The instant specification, however, does not show any working example drawn regions other than WT1 ARR/NRE from WT1 gene.

State of Prior art & Unpredictability:

Vertino et al. (Molecular and Cellular Biology, August 1996, vol. 16, no. 8, pages 4555-4565)[1] discuss the correlation of methylation status in a specific nucleotide sequence for a specific type of cancers, evidencing that empirical experimentation is necessary for diagnosing a specific type of cancer based on a specific nucleotide sequence. Particularly, Vertino et al. discuss the correlation of methylation in *VHL* gene in renal cell carcinomas (page 4555, 1st column, 2nd paragraph), E-cadherin gene in breast and prostate carcinomas (page 4555, 2nd column, 1st paragraph). The need for empirical determination clearly demonstrates the unpredictable nature of the diagnosis employing methylation patterns.

Conclusion:

As discussed above, WT1 spans over 10 exons and is 60,000 nucleotides in length. The instant specification gives guidance/examples pertaining to a method involving only a small fraction of the total length of nucleic acid embraced by the full scope of the claims. Hence, one of skill in the art, in order to practice the invention fully commensurate in scope of the claims, would need to empirically experiment the methylation status of the remaining nucleotides of the entire WT1 gene and determine whether their methylation pattern would be indicative of Wilm's tumor, resulting in an undue amount of experimentation.

Claim Rejections - 35 USC § 102

The rejection of claims 21-23 under 35 U.S.C. 102(b) as being anticipated by Nelson et al. (U.S. Patent No. 5,552,277, issued September 3, 1996), made in the Office Action mailed on December 1, 2005 is withdrawn in view of the Amendment received on August 25, 2005, canceling the claims.

---

[1] Cited previously.

The rejection of claims 7 and 21-23 under 35 U.S.C. 102(b) being anticipated by Duffy (U.S. Patent No. 5,871,917, issued February 16, 1999), made in the Office Action mailed on December 1, 2004 is withdrawn in view of the Amendment received on August 25, 2005, amending claim 7 and canceling the claims 21-23. Duffy et al. do not disclose or suggest a method pertaining to nucleic acid comprising ARR and/or NRE, and therefore would not anticipate the amended claim 7.

Double Patenting

Applicant is advised that should claim 11 be found allowable, claim 23 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. Claim 11 necessarily includes all limitation of the parent claim 7. Hence, claim 11 is drawn to a method of Wilm's tumor diagnosis or cancer prognosis in a subject, wherein the method comprises:

a) determining the methylation state of a nucleotide sequence or sequences comprising WT1 antisense regulatory region (ARR) and/or WT1 negative regulatory element (NRE) in the subject, or in a sample derived from the subject; and

b) concluding therefrom the presence or absence of Wilm's tumor and/or prognosis of cancer in the subject based on the determined methylation state, wherein hypomethylation of the said nucleotide sequence or sequences indicates the presence of Wilm's tumor.

By amendment, claim 23 is identical in scope to claim 11. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

Conclusion

The prior art neither teaches nor suggest for a method of determining cancer prognosis in a subject, wherein the method comprises determining the methylation state of (ARR) and/or WT1 negative regulatory element in the subject, and concluding that hypermethylation of NRE or ARR is positive prognosis, or concluding that hypomethylation of NRE or ARR indicates that the subject is predisposed to relapsing after treatment. The prior art neither teaches nor suggest for a method of diagnosis and/or prognosis determining the methylation state of WT1 NRE and/or ARR employing SEQ ID NO: 1, 2, 3, and 4; or employing SEQ ID NO: 8 or 9.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

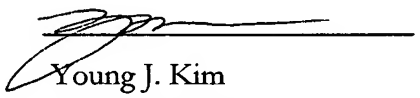
Inquiries

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Young J. Kim whose telephone number is (571) 272-0785. The Examiner is on flex-time schedule and can best be reached from 8:30 a.m. to 4:30 p.m. The Examiner can also

be reached via e-mail to Young.Kim@uspto.gov. However, the office cannot guarantee security through the e-mail system nor should official papers be transmitted through this route.

If attempts to reach the Examiner by telephone are unsuccessful, the Primary Examiner in charge of the prosecution, Dr. Kenneth Horlick, can be reached at (571) 272-0784. If the attempts to reach the above Examiners are unsuccessful, the Examiner's supervisor, Dr. Gary Benzion, can be reached at (571) 272-0782.

Papers related to this application may be submitted to Art Unit 1637 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 CFR 1.6(d)). NOTE: If applicant does submit a paper by FAX, the original copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED, so as to avoid the processing of duplicate papers in the Office. All official documents must be sent to the Official Tech Center Fax number: (571) 273-8300. For Unofficial documents, faxes can be sent directly to the Examiner at (571) 273-0785. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (571) 272-1600.



Young J. Kim
Patent Examiner
Art Unit 1637
11/18/2005

YOUNG J. KIM
PATENT EXAMINER

yjk